

## **REMARKS**

Claims 24-39 are rejected. Claims 1-23 and 40 are withdrawn from consideration. Claims 1-40 are presently pending in the application. Favorable reconsideration of the application in view of the following remarks is respectfully requested.

### **Rejection Of Claims 24-39 Under 35 U.S.C. §103(a):**

The Examiner has rejected Claims 24-39 under 35 U.S.C. 103(a) as being unpatentable over Rembaum et al. (US 4,929,400) in view of Mihara et al. (US 4,331,444) and de Jaeger et al. (US 4,837,168), indicating that Rembaum et al. disclose polymeric microspheres adapted to be used for immunoassays and a method for producing them, the microspheres are acrylic and can range from 1000 Angstroms to 100 microns in size, each microsphere comprises functional groups (i.e. aldehyde) capable of binding proteins and a dye for visually detecting the microspheres. The Examiner indicates that the reference to Rembaum does not disclose that the dye comprises a photographic couple, but De Jaeger et al. disclose latex label adapted to be used for immunoassays in which the latex particles are coupled to dye-forming couplers that can be developed to form cyan, magenta or yellow dyes, the dyes are used to visually detect the occurrence of a reaction of interest, and the reference discloses that phenol or a naphthol type compounds produce cyan dyes, pyrazolone type compounds form magenta dyes and open chain ketomethylene type compounds form yellow dyes. The Examiner further indicates that Mihara et al. disclose a method for immunoassay using a phenol or a naphthol coupler, a pyrazolone coupler, and an open chain ketomethylene coupler that are developed by oxidizing developing agents to form cyan, magenta or yellow dyes, respectively and that the couplers are dissolved in high boiling solvents, making it obvious to one of ordinary skill in the art to dye the microspheres disclosed by Rembaum et al. with the dye-forming couplers dissolved in high boiling solvents disclosed by Mihara et al. and de Jaeger et al. since the 3 dye colors provide versatility and diversity in detection.

Rembaum discloses a process for the production of polymeric particles and, more particularly, evenly sized, magnetic or non-magnetic, microspheres by the polymerization of falling or suspended uniformly- sized and shaped droplets in a containerless environment. The polymeric microspheres with very precise size and a wide variation in monomer type and properties are

produced by deploying a precisely formed liquid monomer droplet, suitably an acrylic compound such as hydroxyethyl methacrylate into a containerless environment. The droplet which assumes a spheroid shape is subjected to polymerizing radiation such as ultraviolet or gamma radiation as it travels through the environment. Rembaum fails to disclose a microsphere loaded with both a photographic coupler and a high boiling organic solvent.

Mihara et al. discloses a method photochemically analyzing in a quantitative manner trace components utilizing immune reaction by marking or labeling an antigen or antibody with a marker. An immune reaction is caused using an antigen or antibody marked with a fogging agent for silver halide, the labeled antigen or antibody is separated from the labeled antigen-antibody reaction product, the silver halide is developed in the presence of either one of the labeled antigen or antibody and the labeled antigen-antibody reaction product, and the density obtained is measured. The method is comparable to radioimmunoassay in having high reproductibility and sufficient sensitivity but does not involve any risk due to radiation. In Mihara, the coupler is dissolved into a high boiling organic solvent and dispersed in a gelatin binder along with silver halide particles, to provide a silver halide particle tagged with a fogging agent/biological probe complex and coupler, all dispersed in a gelatin binder. The coupler is not loaded in a microsphere. In Mihara, the amount of coupler that gets developed into dye depends on the amount of silver halide particles that are fogged by the complex of the antigen and fogging agent that is attached to the surface of the silver halide particles. The color forms as a dye cloud around the exterior of the silver halide particles as development occurs. Mihara fails to disclose microspheres, including a microsphere loaded with both a coupler and a high boiling solvent.

DeJaeger et al. relates to a method for the detection of specific binding agents and their corresponding bindable substances by employing a label which is a latex particle which can be visually detected. DeJaeger fails to disclose a microsphere loaded with both a coupler and a high boiling solvent.

The present invention relates to a polymeric particle for use in a microarray comprising polymeric particle, loaded with at least one photographic coupler and high boiling solvent, and having at least one functionally active group that can interact with a biological probe. In the case of the polymer particles of the

present invention, the developer penetrates the microsphere, with the aid of the high boiling solvent, to reach the loaded coupler and the developed coupler, still loaded in the microsphere, produces a colored microsphere. These particles are readily observable in a microscope after they develop color.

To establish a prima facie case of obviousness requires, first, there must be some suggestion or motivation, either in the references themselves, or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references (or references when combines) must teach or suggest all the claim limitations. The level of skill in the art cannot be relied upon to provide the suggestion to combine references. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure. *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998).

The present invention relates to a microsphere loaded with both a photographic coupler and a high boiling solvent. Rembaum discloses polymer microspheres, but fails to disclose microsphere which are loaded, that is, imbibed with, photographic coupler and high boiling solvent. Mihara, which teaches the use of photographic couplers in silver-halide emulsion layers (col. 10, lines 3-4) and the use of solvent, both high and low boiling solvents (see col. 10, lines 6-7, plus lines 14-15), to introduce the couplers into the gelatin layer, fails to mention the introduction of photographic coupler, high boiling solvents, or both photographic coupler and high boiling solvent into a microsphere. DeJaeger teaches microspheres containing photographic coupler, but fails to teach microspheres containing both high boiling solvent and photographic coupler. None of the references discloses a polymeric particle containing a photographic coupler and a high boiling solvent. Particularly, none of the references teach a microsphere loaded with a high boiling solvent. At best, a combination of the references would produce a microsphere containing coupler, which coupler is soluble in high and low boiling organic solvents.

The Examiner states, "*There is motivation for combining the three references. Rembaum et al. disclose polymeric microspheres comprising a dye for visually detecting the microspheres (see lines 26-30, col. 7). The particles*

*disclosed by Rembaum et al. and the claimed invention are distinct in two ways: 1) the dye disclosed by Rembaum et al. differs from the dye of the claimed invention; and 2) the microsphere disclosed by Rembaum et al. lacks a high-boiling solvent.*

*De Jaeger et al. disclose latex particles adapted to be used for immunoassays. The latex particles are coupled to dye-forming couplers that can be developed to form cyan, magenta or yellow dyes. The reference discloses that phenol or a naphthol type compounds produce cyan dyes, pyrazolone type compounds form magenta dyes and open chain ketomethylene type compounds form yellow dyes.*

*In light of the disclosure of de Jaeger et al., it would have been obvious to substitute the dye disclosed by Rembaum et al. with the dye disclosed by de Jaeger et al. because the dye combination disclosed by de Jaeger et al. provides versatility and diversity in detection."*

However, the references to DeJaeger and Rembaum do not mention the presence of solvent, especially a high boiling solvent, in a microparticle.

The Examiner also notes "*Mihara et al. disclose a method for immunoassay using a phenol or a naphthol coupler, a pyrazolone coupler, and an open chain ketomethylene coupler (see line 55 col. 8 - line 43 col. 9). The dyes disclosed by Mihara et al. are identical to the dyes disclosed by de Jaeger et al. Mihara et al. disclose that the couplers can be dissolved in high boiling solvents (i.e. dibutyl phthalate) before the solution is applied to the target substrate or support (see lines 3-25 col. 10).*

*In light of the disclosure of Mihara et al., it would have been obvious to one of ordinary skill in the art to dissolve the dyes disclosed by de Jaeger et al. in dibutyl phthalate and then apply the solution to the microspheres disclosed by Rembaum et al. to simplify the application process of the dyes to the microspheres."*

Again, the references do not mention the presence of solvent, especially a high boiling solvent, in a microparticle. MPEP 2143.01 III indicates that the "fact that references can be combined or modified is not sufficient to establish prima facie obviousness." "Although a prior art device "may be capable of being modified to run the way the apparatus is claimed, there must be a

suggestion or motivation in the reference to do so." 916 F.2d at 682, 16 USPQ2d at 1432.). There is no motivation provided by the references to load high boiling solvent into the microsphere.

Neither is there any likelihood of success. The Examiner indicates that it would have been obvious to one of ordinary skill in the art to dye the microspheres disclosed by Rembaum et al. with the dye-forming couplers dissolved in high boiling solvents disclosed by Mihara et al. and de Jaeger et al. since the 3 dye colors provide versatility and diversity in detection. However, none of the references teach a microsphere containing, specifically, high boiling solvent, and therefore produce no likelihood of success in producing a microsphere containing high boiling solvent. The present specification indicates, "Particles in the sub-micronic range (nominally less than 100 nanometers) are difficult to detect by optical means. In addition, a polymeric bead solvated with a color forming moiety is difficult to develop into color using chemical means." The examples of the present specification indicate that the presence of the high boiling solvent in the microsphere enhances the intensity of the developed color by maximizing developed dye density (pg. 13, lines 21-25), resulting in enhanced penetration of developer into the microsphere, making the small particles easier to detect and individually identify than microspheres containing coupler alone. See Table I, pg. 24. It is the solubility of the developer in the high boiling solvent that results in enhanced color development, not the solubility of the loaded coupler in the high boiling solvent. The cited prior art is silent with regard to the solubility of developer in high boiling solvent, resulting in enhanced color development of coupler loaded in a microsphere in which high boiling solvent is also loaded.

The Examiner states "*There is also likelihood of success in combining the references. The only modification made to the microspheres disclosed by Rembaum et al. is the dyes coupled to the microspheres. One of ordinary skill in the art would have recognized a way to couple the dyes disclosed by de Jaeger et al. and Mihara et al. to the microspheres disclosed by Rembaum et al., especially since the microspheres disclosed by Rembaum et al. comprise functional groups for binding complimentary functional groups.*" However, it is the presence of the high boiling solvent in the microsphere, which results in the improved penetration of developer into the microsphere to reach the dye. The references are silent relating to the penetration of the high boiling solvent into the

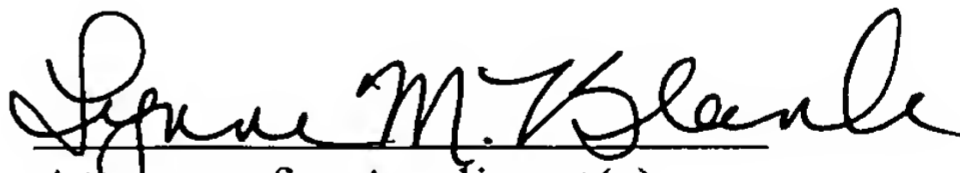
microsphere. The references are also silent regarding the fact that the high boiling solvent is still present when the developer is added, which enhances color development. The references provide no likelihood of success relating to the high boiling solvent loaded in the microspheres, which is key to the improved color development.

As previously discussed, none of the references teach, suggest or disclose a polymeric particle containing a photographic coupler, wherein the microsphere also contains a high boiling solvent. As a result, the references fail to teach all the limitations of the present claims.

Table I, pg. 24 indicates that the use of high boiling solvent provides enhanced color formation - as compared to the use of coupler in microspheres alone. Since the undeveloped coupler is loaded in the microsphere, developer must reach the coupler to produce developed coupler, i.e., color. The presence of high boiling solvent in the microsphere enhances developer penetration, resulting in increased development of the loaded coupler, and enhanced color. The presence of the high boiling solvent in the microsphere, which enhances the penetration of the developer into the microsphere to increase the amount of dye developed, and, hence enhancing the color, is a surprising result, based on the teachings found in the prior art.

It is believed that the foregoing is a complete response to the Office Action and that the claims are in condition for allowance. Applicants respectfully request early allowance to obviate the appeal.

Respectfully submitted,

  
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